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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,893	02/09/2001	Kent Jorgensen	0459-0554P	3281

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	//

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/781,893	Jorgensen
Examiner	**Art Unit**
Gollamudi Kishore	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 11, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11, 14-21, 23, and 24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 14-21, 23, and 24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time and amendment filed on 7-11-03 are acknowledged.

Claims included in the prosecution are 1-11, 14-21 and 23-24.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

2. Claims 1-11, 14-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hong (4,622,392) or Hong (5,484,911) or Peterson (5,827,836) in combination with Janjic (6,229,002) and Vermehren (BBA, 1998) (the references are all of record).

The references of Hong (392), Hong (911), Peterson each discloses phospholipid prodrugs wherein the carbon 1 of the glycerol has an aliphatic chain and the carbon 2 has an organic radical and carbon 3 has a phosphatidyl group . According to the references, the organic radical is released by phospholipase A2. These phospholipids can be in the

form of liposomes (note the abstract, columns 1-6 and Examples of Hong 392; abstract, columns 3-7 and Examples of Hong 911; abstract, columns 7-15 and examples of Peterson).

What is lacking in Hong 392, 911 and Peterson are the teachings of the inclusion of a lipopolymer.

Janjic while disclosing lipid constructs containing PDGF teaches the several advantages of administration of the composition in the form of liposomes and the attachment of PEG to the liposomal surface to shield the liposomal complex from blood proteins and thereby enable it to circulate for extended periods in the blood. According to Janjic, the prodrug is on the outside surface of the liposomes (note the abstract, col. 25, line 5 through col. 28, line 67).

Vermehren while disclosing liposomes containing PEG teaches that PEG not only provide steric hindrance which leads to a decrease in the adsorption and interaction of plasma degrading proteins with the liposomal surface, but also enables PLA2 to have increased catalytic activity on the phospholipid containing liposomes. Based on their studies, Vermehren suggest that one can design and optimize the in vivo degradation of drug loaded liposomes at certain sites, e.g., in extravascular inflammatory tissue due to an enhanced local concentration of the active PLA2 and an accumulation of polymer -grafted liposomes in such tissue (note pages 31-34).

The use of polymer (PEG) containing liposomes for the delivery of the prodrugs of Hong 392, or 911 or Peterson would have been obvious to one of ordinary skill in the art

because the advantages of the liposomes and the ability of PEG to prolong the circulation time of the liposomes and increasing their susceptibility to PLA2 in the host pathological tissue and thereby increasing the release of the drug attached to the carbon 2 of the phospholipids.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that both of the Hong references disclose different compounds than those used in the present invention. This argument is not found to be persuasive since instant claim 1 recites no specific compound, but recites the compounds only in generic terms such as 'organic radical', 'aliphatic group', 'hydrophilic moiety' etc;, followed by functional limitations. Hong references as stated above teaches compounds containing these groups and applicant has not convincingly shown how Hong's compounds are different. Applicant also argues that neither Hong references or Peterson reference describe the mechanism involved in instant invention and that these references fails to disclose features a and d through h. This argument is not found to be persuasive since the primary references of Hong, and Peterson teach compounds lacking only in the lipopolymer and applicant has not convincingly shown that the mechanism of drug release is different from instant mechanism. With regard to applicant's arguments that the references do not teach a and d through h the examiner points out that all three references teach glycerophospholipid compounds and as applicants themselves recognize Hong (911) teaches phospholipase A2. On col. 4, lines 55-62 Hong clearly states the site of action of this

enzyme leading to lyso compound (meets the requirements a, d, e and f). With regard to the limitation g), applicants have not shown that the resultant Hong lyso compounds are not substrate for lysophospholipase. With regard to the limitation h), the examiner points out that the lack of this limitation in the primary references has already been acknowledged by the examiner and that is why Janjic, and Vermehren which provide motivation to include lipopolymer have been combined with those of Hong, and Peterson.

3. Claims 1-11, 14-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozak (6,166,089) of record in combination with Janjic (6,229,002) and Vermehren (BBA, 1998) of record.

Kozak discloses phospholipid prodrugs wherein the carbon 1 of the glycerol has an aliphatic chain and the carbon 2 has an organic radical and carbon 3 has a phosphatidyl group . According to Kozak the organic radical is released by phospholipase A2 present in the pathological tissue (note the abstract, col. 4, line 41 through col. 11, line 9, Examples and claims).

What is lacking in Kozak is the inclusion of a lipopolymer and the administration of the composition in the form of liposomes.

Janjic while disclosing lipid constructs containing PDGF teaches the several advantages of administration of the composition in the form of liposomes and the attachment of PEG to the liposomal surface to shield the liposomal complex from blood proteins and thereby enable it to circulate for extended periods in the blood. According to

Janjic, the prodrug is on the outside surface of the liposomes (note the abstract, col. 25, line 5 through col. 28, line 67).

Vermehren while disclosing liposomes containing PEG teaches that PEG not only provide steric hindrance which leads to a decrease in the adsorption and interaction of plasma degrading proteins with the liposomal surface, but also enables PLA2 to have increased catalytic activity on the phospholipid containing liposomes. Based on their studies, Vermehren suggest that one can design and optimize the in vivo degradation of drug loaded liposomes at certain sites, e.g., in extravascular inflammatory tissue due to an enhanced local concentration of the active PLA2 and an accumulation of polymer -grafted liposomes in such tissue (note pages 31-34).

The use of polymer (PEG) containing liposomes for the delivery of the prodrug of Kozak would have been obvious to one of ordinary skill in the art because the advantages of the liposomes and the ability of PEG to prolong the circulation time of the liposomes and increasing their susceptibility to PLA2 in the host pathological tissue and thereby increasing the release of the drug attached to the carbon 2 of the phospholipid in Kozak.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicants previously argued that Kozak teaches away from formulating the prodrugs into liposomes as evident from col. 6, lines 4-6. In response the examiner pointed out that the reason for Kozak's teachings of not to use liposomes is because the liposomes are taken up by the reticuloendothelial system (RES), (liver, macrophages). However, both

references of Janjic and Vermehren teach the purpose of linking PEG to the lipid (lipopolymer), that is increase in circulation time of the liposomes without being taken up by the RES. Therefore, one of ordinary skill in the art would be motivated to use liposomes in Kozak for the art known advantages of liposomes and attach PEG to the phospholipid forming the bilayer membrane of the liposomes in order to increase the circulation time of the liposomes and avoiding the RES. Applicants' continued argument that the examiner 's comment clearly indicates that Kozak teaches against the use of liposomes is not valid. Applicants argue that Kozak fails to describe features a, d, f, g and (I) . These arguments are not found to be persuasive. On col. 5, lines 9-13 Kozak clearly teaches that one of the preferred embodiments is that the prodrug is scission sensitive to phospholipase A2. Phospholipase A 2 is a specific enzyme attacking a specific site in a glycerophospholipid and therefore, instant limitations a, d and f. With regard to the limitation g, applicants have not convincingly shown that the lysolipid of Kozak is not a substrate for lysophospholipase. With regard to lack of (I) in Kozak as argued by applicants, the examiner is confused as to what this limitation is. Applicants' arguments that the features that are missing in Kozak are not disclosed in Janjic and Vermehren since they do not relate to anti-cancer lysolipids as part of lipid prodrug are not found to be persuasive since motivation to use PEG lipopolymer need not be the same as applicants'.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

September 23, 2003